UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION	**MDL No. 2875**
THIS DOCUMENT RELATES TO ALL CASES	**HON. ROBERT B. KUGLER** **CIVIL NO. 19-2875 (RBK)**

PLAINTIFFS' BRIEF IN OPPOSITION TO DEFENDANTS' MOTION TO EXCLUDE THE GENERAL CAUSATION OPINION OF PLAINTIFFS' EXPERT STEPHEN S. HECHT, PH.D.

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PRELIMINARY STATEMENT

Stephen S. Hecht, Ph.D. is a respected authority with regard to the carcinogenicity of nitrosamines, having begun his scientific research into this subject in the 1970s. Dr. Hecht has been a front-line researcher and author of peer-reviewed literature regarding the carcinogenicity of nitrosamines for decades. Dr. Hecht's qualifications and knowledge base to opine on this subject cannot be reasonably disputed, which likely explains why the Defendants say nothing about his background. Defendants also fail to acknowledge or contend with the fact that Dr. Hecht's methodology supporting his opinion that the NDMA and NDEA contaminated valsartan is capable of causing/increases the risk of cancer, is rooted in his scientific research and the peer-reviewed literature, which are the touchstones of methodological validity.

This shotgun *Daubert* motion, like the others filed by the defense, is set against the backdrop of a well-established scientific and regulatory consensus that NDMA and NDEA are probable human carcinogens. Dr. Hecht's opinions fall directly in line with the weight of authority, grounded upon the scientific evidence across animal studies, human mechanistic studies, human dietary studies, occupational studies, and the few human epidemiology studies evaluating health claims data of users of valsartan. Every category of evidence and the most prominent studies were considered. Dr. Hecht took all of this into account and his opinions are directly in line with this body of peer-reviewed scientific literature, some of which he authored years prior to this litigation. Defendants ignore this and resort to mischaracterizations of Dr. Hecht's opinions, partial citations, and hyper-technical but inconsequential attacks on Dr. Hecht's methodology, which is steeped in research and peer-reviewed literature.

In essence, the defense previews a cross-examination that would go to the weight of the conclusions reached, at most, but in no way would establish that Dr. Hecht failed to apply an

acceptable scientific methodology. The motion should be denied.

STATEMENT OF FACTS

NDMA and NDEA are probable human carcinogens, and should be treated "for all practical purposes" as causing cancer in humans. (Internal Agency for Research on Cancer, *Some N-Nitroso Compounds*, in *IARC Monogr. Eval. Carcinog. Risk Chem. Hum.*, 107, 152 (Lyon, Fr. 1978), Ex. 1).[1,2] The World Health Organization's 2002 peer-reviewed publication addressing the carcinogenicity of NDMA concluded:

> DNA adducts (in particular, O6-methylguanine) formed by the methyldiazonium ion generated during metabolism likely play a critical role in NDMA carcinogenicity. Observed variations in carcinogenicity among species and strains correlate well with variations in activity of O6-methylguanine DNA-methyltransferase. Putative pathways for the metabolism of NDMA are similar in rodents and humans, and indeed the formation of O6-methylguanine has been detected in human tissues exposed to NDMA.
>
> **Therefore, owing to the considerable evidence of carcinogenicity of NDMA in laboratory species, evidence of direct interaction with DNA consistent with tumour formation, and the apparent lack of qualitative species-specific differences in the metabolism of this substance, NDMA is highly likely to be carcinogenic to human**s.

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[1] Unless otherwise noted, all exhibits are from Adam M. Slater's Certification in Support of Plaintiffs' Opposition to Defendants' Motion to Exclude the General Causation Opinion of Stephen S. Hecht, Ph.D.

[2] The FDA has concluded that "NDMA and NDEA are probable human carcinogens and should not be present in drug products," the EPA considers NDMA and NDEA to be probable human carcinogens, and USP has said, "their presence in medicines, even at trace level is considered unacceptable because Nitrosamine impurities are probable human carcinogens." (FDA, *FDA presents interim limits of nitrosamines in currently marketed ARBs* (Dec. 19, 2018), https://tinyurl.com/4rkpdf5h, Ex. 2; EPA, *N-Nitrosodimethylamine*, https://tinyurl.com/9krh69u9, Ex. 3; EPA, *N-Nitrosodiethylamine*, https://tinyurl.com/48y7nejw, Ex. 4; USP, Summary, Highlights and Timeline of General Chapter <1469> Nitrosamine Impurities (July 20, 2018), Ex. 5). Multiple defense experts also conceded that NDMA and NDEA are probable human carcinogens, as discussed in Plaintiffs' affirmative Daubert briefs. (*See, i.e.*, Pls.' Br. in Supp. of *Daubert* Mot. to Preclude Ops. of Def. Expert Janice K. Britt, p. 4; Pls.' Br. in Supp. of *Daubert* Mot. to Preclude Ops. of Def. Expert Daniel Catenacci, p. 7).

(Liteplo & Meek, *Concise International Chemical Assessment Document 38 – N-Nitrosodimethylamine*, at 23 (2002); Ex. 6, emphasis added (cited in Hecht Report, at 11-12, ECF 1714-3)).

The robust mechanistic support for human carcinogenicity in the peer-reviewed scientific literature is ignored by Defendants. For example, Dr. Hecht has referred to NDMA in a peer-reviewed article, as "a carcinogenic nitrosamine," and described, "DNA damage by dimethylnitrosamine [NDMA] and NNK." Dr. Hecht discussed the article in his deposition:

> These diazohydroxides or the corresponding diazonium ions react with DNA, producing adducts such as O6-methylguanine, or dGuo, from NDMA and O6-pyridyoxobutyl dGuo (O6-POB-dGuo) from NNK. The roles in carcinogenesis of these and related methyl and pyridyoxobutyl and DNA adducts of NDMA, NNK, and other N-nitroso compounds have been extensively studied.

(Dr. Hecht Dep. Tr., 452:11-459:15, ECF-1714-12 (discussing Wang, Cheng, Villalta, Hecht, *Development of liquid chromatography electrospray ionization tandem mass spectrometry methods for analysis of DNA adducts of formaldehyde and their application to rats treated with N-nitrosodimethylamine or 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone*, CHEM. RES. TOXICOL. 20, 1141-1148 (2007), Ex. 7)). Another study, of "the roles of P450 enzymes in the activation of NDMA and NDEA and tobacco-smoke-related nitrosamines" stated, "There is considerable evidence to support the view that carcinogenic *N*-nitrosamine derivatives are important factors in human cancer, through ingestion by smoking as well as food…Initial oxidation of nitrosamines by P450 enzymes is believed to be critical in metabolic activation to cause cancer in man as well as in experimental animals." (Yamazaki, Inui, Yun, Guengerich, & Shimada, *Cytochrome P450 2E1 and 2A6 enzymes as major catalysts for metabolic activation of N-nitrosokealkylamines and tobacco-related nitrosamines in human liver microsomes,*

CARCINOGENESIS 13, 1789, 1792 (1992), Ex. 8).

A study of human liver specimens after a fatal case of presumed NDMA poisoning, stated in part:

> The results indicate for the first time that humans, like rodents, appear to activate dimethylnitrosamine metabolically to a strong methylating agent, resulting in methylation of liver DNA at both the 7- and O6 positions of guanine.
>
> * * *
>
> Both rats and humans, then, appear capable of metabolically activating DMN to a strong methylating agent, which interacts with the same sites in liver DNA in both species.

(Herron & Shank, *Methylated purines in human liver DNA after probable dimethylnitrosamine poisoning*, CANCER RESEARCH 40, 3116-3117 (1980), Ex. 9). Dr. Hecht explained the significance: "**Yes, absolutely it is significant because it shows that in a human you are getting the same types of DNA damage from dimethylnitrosamine that you get in a rat. It is very significant**." (Dr. Hecht Dep. Tr., 460:4-462:2).

Another peer-reviewed article analyzed multiple "lines of evidence," including "Comparative in vitro metabolism" and "Studies with cultured human tissues and cells" confirming in part that NDMA and NDEA "were metabolized in all tissues examined." The authors concluded: "There is now convincing evidence that the biological activity of *N*-nitroso compounds in humans does not differ substantially from that in experimental animals. **We can therefore predict with a high degree of confidence that *N*-nitroso compounds including nitrosamines are carcinogenic in man**." (Archer, *Mechanisms of action of N-nitroso compounds*, CANCER SURVEYS 8, 241-250 (1989), Ex. 10; *see also* Anderson, Souliotis, Chhabra, Moskal, Harbaugh, & Kyrtopoulos, *N-nitrosodimethylamine-derived O(6)-methylguanine in DNA of monkey gastrointestinal and urogenital organs and enhancement by ethanol,* INT. J. CANCER 66,

130-4 (Mar. 1996) (in discussing a study with monkeys: "Thus primate tissues, especially those of the gastrointestinal and urogenital organs, are sensitive targets for DNA adduct damage due to NDMA, and ethanol co-exposure leads to striking increases in adducts. **Our data support epidemiology implicating nitrosamines in causation of cancers of stomach and other organs, and alcohol as enhancing internal exposure to nitrosamines.**") (emphasis added)), Ex. 11).

Dr. Hecht took the relevant categories of scientific evidence into account and landed in the same place as IARC. In the absence of human studies that cannot ethically be performed with, "exposure to NDMA or NDEA in the absence of other possibl[e] causes," the substances cannot be classified as Class 1 known proven human carcinogens, thus each "should be regarded for practical purposes as if it were carcinogenic to humans." (Dr. Hecht 8/17/21 Dep. Tr., 143:3-8).

Defendants and their 30(b)(6) witnesses agree, having conceded that these substances are probable human carcinogens, and that the NDMA and NDEA in the contaminated valsartan increased the risk of cancer. For example, ZHP stated through Prinston and Solco, in announcing the recall, "[redacted]."[3] Likewise, the ZHP Deviation Investigation Report ("DIR") for the TEA process, which was submitted to the FDA, stated: "[redacted]." (PRINSTONO0075850, Ex. 13), emphasis added. ZHP 30(b)(6) witness Min Li, Ph.D. conceded that NDMA and NDEA are "probable human carcinogens,"[4] and that [redacted]

[3] (SOLCO00024226, Ex. 12).

[4] (Min Li 4/22/21 Dep. Tr., 696:3-697:10, Ex. 14).

[redacted]."[5] Similarly, Hetero's 30(b)(6) witness conceded that the NDMA contamination increased the risk of cancer for the people who took those contaminated pills. (B.V. Ramarao 4/29/21 Dep. Tr. 377:5-20, Ex. 16 (cited in Hecht Report at 13)).

A. Dr. Hecht's Background and Qualifications.

Dr. Hecht's background and qualifications are set forth in detail in his report and the attached CV, and are summarized here. (Dr. Hecht Report at 1-6; Dr. Hecht CV, Ex. 17). Dr. Hecht holds a Ph.D. from MIT, and held, "a postdoctoral fellowship position at MIT in the laboratory of Professor Klaus Biemann, a pioneer in the application of mass spectrometry to organic chemical analysis."[6] Dr. Hecht has "carried out research related to nitrosamines continually since 1973," his research was "the first to characterize 'tobacco-specific nitrosamines' in tobacco products," and his "research paper in the 1978 Journal of the National Cancer Institute, describing these compounds, has been cited by the American Association for Cancer Research as a 'Landmark in Cancer Research.'" Dr. Hecht has worked in an academic and research setting since 1996:

> In 1996, I relocated to the University of Minnesota where I hold my current position as Wallin Professor of Cancer Prevention, a "Land Grant Endowed Chair" in cancer prevention research. My academic appointment is in the Department of Laboratory Medicine and Pathology, in the University of Minnesota Medical School. I am also a member of the Medicinal Chemistry and Pharmacology graduate programs. From 1998-2014, I was the founding Head of the Carcinogenesis and Chemoprevention Program of the Masonic Cancer Center, University of Minnesota, a National Cancer Institute designated Comprehensive Cancer Center. I currently lead a research group of 10-15 scientists with B.S., M.S., or Ph.D. degrees in the chemical and biological sciences. Our research, which focuses on mechanisms and prevention of cancer induced by tobacco products and environmental agents, is fully funded by

[5] (*Id.* at 647:9-648:5 (cited in Dr. Hecht Report, at 12)).

[6] Mass spectrometry is the method used to identify the NDMA and NDEA in the contaminated valsartan.

> grants from the U.S. National Cancer Institute and the National Institute of Environmental Health Sciences. I am the principal investigator of three R01 grants and a program project (P01) grant, from the National Cancer Institute and co-investigator on a number of other grant and cooperative agreement awards from the National Institutes of Health and the Food and Drug Administration. I have been awarded a Merit Award (10 years of funding) and an Outstanding Investigator Grant (14 years of funding) from the National Cancer Institute.

(Dr. Hecht Report, at 2-3). Dr. Hecht also "served as Editor-in-Chief of the American Chemical Society journal *Chemical Research in Toxicology* from 2013-2017 and as an Associate Editor of the *Journal of Medicinal Chemistry* from 2004-2012." He has also, "served on multiple writing groups for the International Agency for Research on Cancer Monographs on the Evaluation of Carcinogenic Risks to Humans." (Dr. Hecht Report, at 3). Dr. Hecht's contributions to the peer-reviewed scientific literature are summarized in his report:

> I have published over 880 original manuscripts, book chapters, reviews, and other peer reviewed documents in the scientific literature. This includes more than 600 original research articles in peer-reviewed journals. More than half of these original research articles are concerned with nitrosamines, including nitrosodimethylamine (NDMA), also known as dimethylnitrosamine (DMN). My H index is 91, and my articles have been cited more than 35,000 times.
>
> My first publication on nitrosamines was in 1974 when my colleagues and I discovered N'-nitrosonornicotine (NNN) in smokeless tobacco. This was the first example of a carcinogenic nitrosamine in unburned tobacco; in fact, the first example of any carcinogen in unburned tobacco. This paper was published in Science, and revolutionized the characterization and carcinogenicity assessment of tobacco products.

(Dr. Hecht Report, at 4). Dr. Hecht's research studies have included evaluation of "the carcinogenicity of nitrosamines including tobacco-specific nitrosamines, cyclic nitrosamines, and other nitrosamines found in consumer products. We then extended our studies to investigate the metabolism of nitrosamines in laboratory animals and humans…. Our group characterized most

of the DNA adducts formed by tobacco-specific nitrosamines and related cyclic nitrosamines." (Dr. Hecht Report, at 5). In addition:

> Thus, as a result of more than 45 years of research in chemical and tobacco carcinogenesis, much of it focused on nitrosamines, I am thoroughly familiar with the state of the art in the formation, quantitative analysis, chemistry, biochemistry, metabolism, carcinogenicity, human exposure biomarkers, and DNA damage by nitrosamines. I currently serve on the European Food Safety Authority panel evaluating nitrosamines in food. I also served on the expert panel for the FDA Workshop entitled "Nitrosamines as Impurities in Drugs: Health Risk Assessment and Mitigation Public Workshop," March 29, 2021.

(Dr. Hecht Report, at 6; Dr. Hecht Dep. Tr., 155:16-24).

B. Dr. Hecht's General Causation Opinion and Methodology.

Defendants provide a grossly misleading picture of Dr. Hecht's methodology and opinions. First, Defendants pretend that Dr. Hecht's sole opinion is that the ingestion of the contaminated valsartan is just a risk factor for cancer. (Defs.' Br. at 48-49 (citing Dr. Hecht Dep. Tr., 26:9-13, 30:10-13)). The "risk factor" testimony was part of a series of questions and answers where the defense attorney went through a list of "risk factors" for cancer and listed family history, tobacco use, alcohol, and obesity. He then confirmed that "increased nitrosamine intake is a risk factor for cancer." (Dr. Hecht Dep. Tr., 25:23-26:13).

Dr. Hecht testified that the general causation question is whether the contamination of the valsartan at issue, "can cause cancer in humans." (Dr. Hecht 8/17/21 Dep. Tr. at 28:23-29:16). It is his opinion, "that nitrosamines in valsartan-containing medication increase the risk of causing cancer." (Dr. Hecht 8/17/21 Dep. Tr. at 166:1-5). He later testified to his agreement with the opinion set forth in the peer-reviewed 2002 WHO publication addressing the carcinogenicity of NDMA, that "NDMA is highly likely to be carcinogenic to humans." (Dr. Hecht Dep. Tr. at 492:25-493:16). This is fully consistent with the opinions set forth in his report that "**the NDMA**

and NDEA levels found in the contaminated valsartan were completely avoidable and therefore are and **were unreasonably dangerous, causing an increased risk for the development of cancer for those people ingesting the contaminated valsartan**," and "The exact same DNA adducts and mutations are found in human tissues exposed to NDMA in vitro**. Given sufficient exposure to NDMA and NDEA, as with the levels found in the contaminated valsartan (see below), the formation of these DNA adducts would be sufficient to cause mutations and cancer in exposed humans**." (Dr. Hecht Report, at 1, 11 (emphasis added)). Moreover, ZHP 30(b)(6) witness Min Li, Ph.D. confirmed that this question could not be directly studied in humans, as it "would be unethical to knowingly give NDMA to humans, as a result of the risk of cancer," and more specifically, **it "would be unethical 'to give humans NDMA in the levels that were found in the valsartan pills**.'" (Dr. Hecht Report, at 12).

The defense also mischaracterizes Dr. Hecht's methodology, which was founded on consideration of each category of relevant scientific evidence in the peer reviewed literature. Defendants nit-pick at inconsequential issues, as they point out that Dr. Hecht did not personally perform experiments regarding the contaminated valsartan, agreed that association does not automatically equate to causation, agreed he did not apply Bradford Hill, and could not point to studies establishing NDMA and NDEA as "known causes of cancer" (since no studies can be ethically conducted to deliberately administer the carcinogenic substances to humans) (Def. Br. at 41-43). These isolated, non-determinative sound bites are of no moment.

Defendants incredibly misrepresent that, "Dr. Hecht's report and testimony is nothing more than his subjective belief, unsupported by any peer-reviewed literature or study." (Def. Br. at 45). Of course, Dr. Hecht's report and deposition testimony are steeped in peer-reviewed literature. Dr. Hecht evaluated "the totality of the evidence," and applied a fundamentally valid methodology:

> I take into consideration the high carcinogenicity of NDMA in animal models able to induce tumors and I think something like 28 different animal species, even at very low doses as shown in rats. I combine that with the study design of the prospective studies and the very reliable dietary information on NDMA in food and I conclude that this is collectively a very strong link.
>
> * * *
>
> I'm familiar with the methodology for the analysis of nitrosamine in foods and I know that there are very good, very thorough databases on nitrosamines in food.
>
> I'm familiar with the methodology used in epidemiology prospective so-called cohort studies. I'm familiar with those things and I'm also familiar with the animal data on nitrosamines and the dose response data for dimethyl and several other nitrosamines from animal studies. So I'm very familiar with all of this literature.
>
> It doesn't -- it's not something that I just started reading about, you know, to prepare for this deposition. This is something I have been involved with for more than 45 years, so I'm quite familiar with the field. I watched the field evolve. I'm familiar with the evolution of all of the animal data and the evolution of all of the analytical chemistry data which in the early days was plagued by artifacts and other problems, but now is known to be extremely reliable.
>
> So when I put all of this data together and looking at it in comparison, looking at it in context of the firm highly reliable data that we have, put that together with the use of an epidemiologic study design, with the cohort study, I'm quite confident in the results of these studies and after having reviewed them all, my conclusion is that yes, there is definitely causation. That's my conclusion.

(Dr. Hecht Dep. Tr., 248:7-23, 250:6-251:14). Defendants cease upon an isolated statement just after the above-cited testimony, that this was not a "formal evaluation." Of course, counsel failed to ask what that meant, and it obviously does not mean that Dr. Hecht did not apply a valid methodology because his testimony demonstrates that he did so.

LEGAL ARGUMENT

I.

DR. HECHT'S METHODOLOGY IS RELIABLE

The Third Circuit, "made clear in *Paoli II,* an expert's level of expertise may affect the reliability of the expert's opinion." *Elcock v. Kmart Corp.*, 233 F.3d 734, 746 (quoting *In re Paoli R.R. Yard PCB Litigation*, 35 F.3d 717, 741 (3d Cir. 1994)). *Daubert* requires that an expert, "employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Elcock*, 233 F.3d at 746 (3d Cir. 2000) (quoting *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999)). Dr. Hecht's extensive expertise in the study of the carcinogenicity of nitrosamines, documented and rooted in the peer-reviewed literature, establishes the reliability of his methodology. *Geiss v. Target Corp.*, No. 09–2208 (RBK/KMW), 2013 WL 4675377, at *4 (D.N.J. 2013) (quoting *Elcock v. Kmart Corp.*, 233 F.3d 734, 745-47 (3d Cir. 2000) (Ex. 18)). This is especially true since, "Rule 702 has a liberal policy of admissibility." *Geiss*, 2013 WL 4675377 at *4 (citing *Pineda v. Ford Motor Co.*, 520 F.3d 237, 243 (3d Cir. 2008), other citations omitted.

Dr. Hecht applied the weight of evidence methodology, taking into account the full spectrum of scientific evidence relevant to the issue, including peer-reviewed animal studies, mechanistic studies, human dietary studies, occupational exposure studies, the recently published epidemiological literature addressing people who used valsartan, and binding 30(b)(6) admissions from Defendants.[7] This is a well-accepted methodology in the Third Circuit: "[W]e accept that

[7] This stands in stark contrast to the defense experts, who almost uniformly failed to consider the cross-section of significant categories of scientific evidence directly relevant to the question of general causation, and ignored the damaging admissions by Defendants, which Plaintiffs have highlighted in the *Daubert* motions challenging defense experts' opinions.

the Bradford-Hill and weight of evidence analyses are generally reliable." *In re Zoloft (Sertraline Hydrochloride) Products Liability Litigation*, 858 F.3d 787, 796-797 (3d Cir. 2017), citing *Milward v. Acuity Specialty Products Group, Inc.*, 639 F.3d 11, 17 (1st Cir. 2011).

In *Milward*, the Court reversed the District Court's exclusion of an expert who applied the weight of evidence methodology. The Court observed that in applying weight of evidence: "[T]he use of scientific judgment is necessary," and, "The hallmark of the weight of the evidence approach is reasoning to the best explanation for all of the available evidence." *Milward*, 639 F.3d at 19, 23. Similar to here, the expert in question, "relied on his knowledge and experience in the field…and considered five bodies of evidence drawn from the peer-reviewed scientific literature on benzene and leukemia." This included, as here, extensive mechanistic evidence. *Milward*, 639 F.3d at 19-20. The District Court's error was in usurping the jury "based on its evaluation of the weight of the evidence," where the expert, similar to Dr. Hecht, considered each category of evidence alone and in concert to reach his conclusion and "employed the same level of intellectual rigor that he employs in his academic work." *Milward*, 639 F.3d at 20, 22-26. In *Zoloft,* the Court observed with regard to the application of the weight of evidence in that litigation that "the particular combination of evidence considered and weighed here has not been subjected to peer review." *Zoloft*, 858 F.3d at 797. Here, the evidence relied on is peer-reviewed, and Dr. Hecht conducted a similar analysis to the peer-reviewed weight of evidence methodology applied by the WHO in addressing the question of human carcinogenicity. (*See* Dr. Hecht Report at 7-17; Dr. Hecht Dep. Tr., 486:6-494:15).

Dr. Hecht's appropriate application of this methodology is illustrated by his discussion of the weight of evidence in the context of one of the human dietary studies,[8] including consideration

[8] (Knekt, Järvinen, Dich, & Hakulinen, *Risk Of Colorectal Cancer And Other Gastro-*

of the positive and negative findings, consistency with the animal studies, and consistency with the human mechanistic studies:

> It means the relative risk for colorectal cancer is 2.12, so if the CI, 95 percent confidence interval, if it is greater than 1, then it is statistically significant, so, you know, the 1.04 to 4.33 indicates that this 2.12 is statistically significant, so it means a higher relative risk, for the highest versus the lowest intake of NDMA and occurrence of colorectal cancer. It is a significant one.
>
> * * *
>
> So you follow them for years and then you compare the incidence of cancer to the dietary data. That's what they did here. So it is a strong study design, it is a large study, and they have good, solid data.
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> * * *
>
> They did organ culture studies, in vitro studies with human colonocytes, Autrup did that in the '70s by incubating the colonocytes with NDMA, and then they isolated DNA from the colonocytes and analyzed for O6-methylguanine and other DNA, I guess 7-methylguanine, and, you know, they got a positive result. So that was compared to a control, you know, where you have NDMA with colonocytes that have been killed so that there is no metabolism or simply the colonocytes without the NDMA.
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> * * *
>
> Very convincing data. I mean, by current-day standards, the techniques were a little different, but the result is the same.
>
> * * *
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> I mean, the human metabolism of nitrosamines study by Autrup and Harris and others in the late 1970s was very significant because it showed that human tissues could metabolize nitrosamines. I mean, that wasn't known before then, because all the studies had been done in rats, so as we discussed repeatedly during these sessions, metabolism is absolutely required for the carcinogenicity of dimethylnitrosamine. These studies demonstrated that clearly back

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Intestinal Cancers After Exposure to Nitrate, Nitrite and N-Nitroso Compounds: A Follow-Up Study, INT. J. CANCER 80, 852-856, at 855 (1999), Ex. 19).

> in the '70s, and everything that has been done since then is consistent with that.
>
> * * *
>
> Because here they used human tissues to show that human tissues were capable of metabolizing NDMA and NDEA. As we said before, metabolism is required for the carcinogenicity of NDMA, and so, you know, at that time questions still existed whether human tissues could metabolize NDMA, and these studies by Autrup, Harris, and others showed that they could.
>
> Even colonocytes, that's significant with respect to this particular study by Knekt, because that's where they found the higher risk for cancer in the colon, colorectal.

(Dr. Hecht Dep. Tr., at 440:18-451:22).

Defendants cannot nearly meet the standard for exclusion: "A court should not, however, usurp the role of the fact-finder; instead, an expert should only be excluded if the flaw is large enough that the expert lacks the 'good grounds' for his or her conclusions." *Zoloft*, 858 F.3d at 792-793. In the *Xarelto* litigation, a series of *Daubert* motions was summarily denied. The Court found that the plaintiffs' experts applied a proper methodology, relying on peer-reviewed literature, thus the balance of the defense's criticisms went to the weight of the opinions, not admissibility. *See In re Xarelto (Rivaroxaban) Prod. Liab. Litig.*, No. 2:14-MD-02592, 2017 WL 1352860 (E.D. La, Apr. 13, 2017) (Ex. 20). A similar conclusion is appropriate here.

A. Dose and Duration of Use.

Dr. Hecht clearly considered the impact of dose and duration of use. This begins with his cataloguing of the contamination levels in his report, and the time periods during which the manufacturers sold the contaminated valsartan. (Dr. Hecht Report, at 21-26; Dr. Hecht Dep. Tr., 553:16-554:10, 564:12-567:7). Dr. Hecht placed the contamination levels found in Defendants' drugs in context with the literature. In discussing a meta-analysis regarding dietary literature, he

discussed a demonstrated dose-quantified increased risk of gastric cancer: "**When daily NDMA intake reached 0.12 ug, the harmful effect to human became more obvious. For perspective, 0.12 ug (micrograms) is equivalent to 120 ng (nanograms), and in a 320 mg dose of valsartan would equate to 0.375 ppm. These levels are in line with the levels established by the FDA, and were exceeded by the vast majority of the valsartan tested for nitrosamine contamination**." (Dr. Hecht Report, at 15-16, discussing Song, Wu, & Guan, *Dietary Nitrates, Nitrites, and Nitrosamines Intake and the Risk of Gastric Cancer: A Meta-Analysis*, NUTRIENTS 7, 9872-95, at 9892-9893 (2015), Ex. 21). Of course, the defense asked Dr. Hecht no questions about this important scientific evidence and ignored it in their motion. Dr. Hecht concluded in his report: "In general, the increased risk would likely be commensurate with the contamination levels, dosages, and periods of use. Therefore, people who ingested the valsartan with higher contamination levels and larger doses, over longer periods of time, would likely have a more substantial increased risk as opposed to those who ingested valsartan with lower contamination levels and lower doses, and for shorter periods of use." (Dr. Hecht Report, at 27).

Defendants also suggest that Dr. Hecht conducted no research regarding a potential threshold dose for humans, as if he was required to perform such a study – and as if the scientific evidence pointed to a threshold dose for NDMA and NDEA. (Def. Br. at 34). The dietary literature cited just above speaks directly to the impact of dose for humans, which is the key question. Moreover, the defense argument is misleading because the cited testimony addresses a narrower and non-dispositive issue—the fact that Dr. Hecht did no **original** research on human dose threshold. (Dr. Hecht Dep. Tr., 81:11-82:3). He similarly agreed to the irrelevant fact that he did no risk assessment calculations, since that is not his expertise. Instead, he deferred to the risk assessment that yielded the levels set by the FDA, as well as the peer reviewed literature including

the dietary data showing increased harm at quantified levels of NDMA. (Dr. Hecht Dep. Tr., 167:6-22). *See Paoli*, 35 F.3d at 794 (noting that a regulatory risk assessment identifying incremental cancer risks, used by all three of plaintiffs' experts, "is important and will be of aid to the plaintiffs," and finding expert opinions admissible). He confirmed that "dose response is very important in carcinogenesis. You know, this Gombar study was published before the Peto study, if I'm not mistaken. So, I mean, we do know a lot about the dose response characteristics of NDMA in laboratory animals, particularly rats. Also mice and hamsters…." (Dr. Hecht Dep. Tr., 341:5-22). He also testified regarding the impact of a low dose on bioavailability. (Dr. Hecht Dep. Tr., 342:22-343:14). Thus, dose was clearly considered. Moreover, original research is not required to validate an expert, nor is an expert required to cover every aspect of a causation analysis such as performing an independent risk assessment.

In a further effort to obscure Dr. Hecht's consideration of the impact of dose on carcinogenicity, Defendants pretend that his entire opinion is that there is no safe dose. On the contrary, the opinion starts with there being no "threshold for carcinogenicity," an opinion based on the literature, "I believe there is no threshold based on the studies of Peto, Grasso and others. The large rat dose response study. They concluded that there was no indication of a threshold." (Dr. Hecht Dep. Tr., 369:9-370:2). Dr. Hecht also addressed acute vs. chronic usage: "it would be more likely from continuous use, because, you know, the cumulative dose would be greater." (Dr. Hecht Dep. Tr., 391:2-11). Finally, he explained, with reference to the landmark Peto study relied on by the FDA to perform the risk assessment that established the applicable limits, "**we know that very low doses of NDMA given over a long period of time to rats can cause a significant incidence of tumors**." (Dr. Hecht Dep. Tr., 391:391:12-392:1).

Defendants apply a faulty legal analysis on top of their wholesale mischaracterization of what Dr. Hecht did, relying heavily on *McClain v. Metabolife Int'l*, 401 F.3d 1233 (11th Cir. 2005), a case that is entirely distinguishable from this one. The Court first distinguished between two types of cases:

> In analyzing the experts' testimony, we note that toxic tort cases usually come in two broad categories: first, those cases in which the medical community generally recognizes the toxicity of the drug or chemical at issue, and second, those cases in which the medical community does not generally recognize the agent as both toxic and causing the injury plaintiff alleges. **Examples of the first type include toxins like asbestos, which causes asbestosis and mesothelioma; silica, which causes silicosis; and cigarette smoke, which causes cancer.** This case, involving Metabolife's combination of ephedrine and caffeine, falls into the second category. The medical community does not generally recognize the toxicity of this drug combination or ephedrine alone as causing the injuries Plaintiffs allege.

Id. at 1239 (emphasis added). *McClain* addressed an herbal supplement and fell into the second category. This case falls into the first category, as there is a broad scientific consensus that NDMA and NDEA are probable human carcinogens. If *McClain* stands for anything relevant to this case, it is that Defendants' experts must meet the heightened bar for overcoming the scientific consensus that NDMA and NDEA can cause cancer in humans. In addition, the excluded expert, "conceded that many people take drugs containing ephedrine at the same time they ingest large amounts of caffeine from coffee, and that the recommended dose of Metabolife 356 contains 72 milligrams of ephedrine, **roughly half the FDA allowable limits on ephedrine**." *Id.* at 1241, emphasis added. The same expert also relied on FDA rules that the agency ultimately withdrew as insufficiently scientific. *Id*. at 1248. None of these issues exist here. Last, the Court noted:

> It is also important to consider what other evidence O'Donnell failed to present that might have supported the reliability of his opinions in this case. **He offered no epidemiological data.** He offered no clinical trials. **He offered no animal studies to support his**

> **opinions.** O'Donnell also offered no long-term studies about the toxicity of the ephedrine/caffeine combination on humans. As even O'Donnell explained: "[l]ong term studies are used for chronic use to determine safety;" still, he offered opinions about the safety of Metabolife in absence of such long-term studies.

Id. at 1251 (emphasis added). Here, where human clinical studies could not be performed, Dr. Hecht considered animal studies, the mechanisms of action by which NDMA and NDEA initiate carcinogenesis in humans, human dietary literature, human occupational literature, and human valsartan epidemiology. Thus, *McClain* in no way supports excluding the opinions of Dr. Hecht.

In addition, the only District of New Jersey case citing *McLain* is *In re Johnson & Johnson Talcum Powder Prods. Liab. Litig.*, 509 F. Supp. 3d 116, 192 n.52, 197 (D.N.J. 2020), for the generic proposition that Courts may consider the *Reference Manual on Scientific Evidence*. In *Talcum*, the Court clearly applied a more nuanced approach regarding dose-response:

> Generally, "while precise information concerning the exposure necessary to cause specific harm to humans and exact details pertaining to the plaintiff's exposure are beneficial, **such evidence is not always available, or necessary, to demonstrate that a substance is toxic to humans given substantial exposure and need not invariably provide the basis for an expert's opinion on causation**." *Westberry v. Gislaved Gummi AB*, 178 F.3d 257, 264 (4th Cir. 1999) (admitting expert testimony that exposure to talc caused sinus problems despite inability to determine threshold level of exposure necessary to cause plaintiff's injuries). Here, the Court acknowledges, as correctly pointed out by Defendants, that strong evidence of dose-response would tend to show a stronger causative relationship between talc use and ovarian cancer. However, based on epidemiological principles, a strong dose-response is not necessarily required for an expert to find a casual nexus. *See, e.g.*, *Ferguson v. Riverside Sch. Dist. No. 416*, No. 00-0097, 2002 WL 34355958, at *6 (E.D. Wash. Feb. 5, 2002) ("The Court determines that the lack of a model for determining causation based on a 'dose-response' relationship does not undermine the reliability of [the expert's] testimony."). Even so, the causation experts have pinpointed studies that demonstrate evidence of dose-response, i.e., meta-analyses, and adequately explained why the studies, themselves, are reliable.

Talcum, 509 F. Supp. 3d at 179. This standard is met here. In addition, Plaintiffs have presented other experts who opine on more granular quantification of the dose-response relationship for NDMA and NDEA to the extent that is necessary, and Plaintiffs' experts do not need to each bear the burden of proving Plaintiffs' entire case individually. *See Id.* at 140-41 (allowing an expert to provide reliable opinions underlying general causation but not general causation itself).

Talcum also speaks to Defendants' reliance on *Pritchard* for the supposed requirement that Plaintiffs prove NDMA and NDEA can double their risk of cancer, (Defs.' Br. 19-20):

> A relative risk of 2.0 means the risk has doubled, "indicating that the risk is twice as high among the exposed group as compared to the non-exposed group." *Magistrini*, 180 F. Supp. 2d at 591. **In epidemiology, there is, however, no threshold, or a magical number, of a relative risk that must be found in order to place significant weight on the strength of association factor. Indeed, "[a] relative risk of 2.0 is not so much a password to a finding of causation as one piece of the evidence, among others for the court to consider in determining whether an expert has employed a sound methodology in reaching his or her conclusion."** *Magistrini*, 180 F. Supp. 2d at 606 (quoting *Landrigan v. Celotex Corp.*, 127 N.J. 404, 419, 605 A.2d 1079 (1992)).
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> **I note that in the context of relative risk, courts have endorsed "a flexible *Daubert* inquiry rather than bright-line rules."** *Pritchard*, 705 F. Supp. 2d at 486 (concluding that "a relative risk of 2.0 is not dispositive of the reliability of an expert's opinion relying on an epidemiology study, but it is a factor, among others, which the Court is to consider in its evaluation"). **Accordingly, in the context of relative risk on a *Daubert* motion, the Court's role is to determine whether the expert has reliably arrived at, based on sound scientific methods, a relative risk that in his or her view could be clinically significant.** *See, e.g.*, *Pick v. Am. Med. Sys., Inc.*, 958 F. Supp. 1151, 1160 (E.D. La. 1997) ("A relative risk above 1.0 is statistically significant, even if not sufficient, by itself, to establish causation by a preponderance of the evidence."); *Miller v. Pfizer Inc.*, 196 F. Supp. 2d 1062, 1079 (D. Kan. 2002) (declining to find, as a matter of law, that a relative risk must be above a certain number to be clinically significant). Of course, the greater the

> relative risk, the stronger an association would be, and indeed, if the relative risk is 2.0, the "agent was more likely than not the cause of an individual's disease." *Magistrini*, 180 F. Supp. 2d at 591.

Talcum, 509 F. Supp. 3d at 163-64 n.37. In fact, as set forth above, the *Knekt* human dietary study yielded a relative risk of 2.12 for colorectal cancer. (Dr. Hecht Dep. Tr., at 440:18-451:22). Dr. Hecht stated, "I would say collectively the papers that we reviewed indicate that NDMA in food does cause cancer. Otherwise, they wouldn't have seen these elevated relative risks in all of these different studies, some of which were very large." (Dr. Hecht Dep. Tr., 245:12-20).

Defendants also cite two cases they present as having rejected the "no threshold model," which argues that "when no safe-threshold of exposure to a carcinogen has been established, each and every exposure will increase the development of cancer." *Henricksen v. ConocoPhillips Co.*, 605 F. Supp. 2d 1142, 1165-66 (E.D. Wa. 2009). However, Dr. Hecht did not simply rely on this assumption without support, and did not rest his analysis solely on this opinion. Instead, Dr. Hecht relied on the peer-reviewed scientific literature and determined that NDMA and NDEA have shown to be carcinogenic at all levels due to their mechanism of action (namely, their ability to damage DNA and institute carcinogenesis). (*See, i.e.*, Peto, Gray, Brantom, & Grasso, *Effects on 4080 rats of chronic ingestion of N-nitrosodiethylamine or N-nitrosodimethylamine: a detailed dose-response study*, CANCER RES. 51, 6415-6451 (1991) (finding, "**The linear relationship observed at low dose rates (below 1 ppm) suggests that** under these experimental conditions, among rats allowed to live their natural life span, a dose of 1 ppm of NDEA or NDMA in the drinking water will cause about 25% to develop a liver neoplasm**, a dose of 0.1 ppm will cause about 2.5% to do so, and a dose of 0.01 ppm will cause about 0.25% to do so, etc., with no indication of any 'threshold.**'"). **Lance Molnar, Ph.D., Mylan's Senior Director, Global Pharmacology and Toxicology, agreed in his deposition that nitrosamines are treated as non-**

threshold by "the EMA, FDA, ICH … regulatory bodies in general" and that "non-threshold effect would mean that a single molecule could be detrimental." (Lance Molnar 5/07/2021 Dep. Tr., 121:22-23, 125:2-6, Ex. 23). Given this scientific support, it is clear that Dr. Hecht did not merely assume that any amount of NDMA or NDEA must be dangerous without adequate scientific basis. Nor was this his only opinion regarding dose, rather it is a facet of his analysis.

B. Dr. Hecht's Incorporation of Animal Studies In His Analysis.

Dr. Hecht relied on the compelling animal study data as part of the support for his opinions on NDMA and NDEA carcinogenicity. This is entirely appropriate as recognized by the Third Circuit in a very similar situation:

> Here, where the EPA has relied on animal studies to conclude that PCBs are a probable human carcinogen, where there is reason to think that animal studies are particularly valuable because animals react similarly to humans with respect to the chemical in question, and where the epidemiological data is inconclusive and some of it supports a finding of causation, we think that the district court abused its discretion in excluding the animal studies.

Paoli, 35 F.3d at 781. The Court also made the highly relevant point that, "The 'more probable than not' standard employed by EPA is the same standard that is employed in civil litigation." *Id.* at 780.

Dr. Hecht succinctly answered the defense's criticism regarding the generally larger doses of NDMA given to animals as compared to the doses in the contaminated valsartan. The defense focused during the deposition on Dr. Hecht's 1986 paper, *Comparative Tumorigenicity of DNA Methylation in F344 Rats by Methylnitrosamino Butanone and Nitrosodimethylamin*e. That study by Dr. Hecht was designed to compare the "NNK and NDMA carcinogenicity and metabolism using the doses of NNK that we knew induced a certain percentage of lung tumors…not designed to look at human doses at all." For context, NNK is a "Class 1 known carcinogen," associated

with smoking. Those given NDMA showed the development of tumors in 20% (6 of 30) of the rats administered NDMA. Dr. Hecht placed this data in context and linked it to other relevant data: "the purpose of this experiment was to compare NNK and DMN – NDMA…The dose – the dose is far higher than a human dose. **If you want to get to human dose, you have to look at the Peto study**." (Dr. Hecht Dep. Tr., 67:10-75:1). All of this data constitutes pieces of the puzzle.

This testimony also demonstrates the soundness of the methodology underlying Dr. Hecht's opinions. He has performed experiments establishing the human carcinogenicity of certain nitrosamines, with the study cited just above demonstrating common mechanisms of action for NDMA and a known carcinogenic nitrosamine. Dr. Hecht's methodology is an example of the touchstone against which *Daubert* measures the reliability of an expert's methodology. *Kumho*, 526 U.S. at 152 (a Court must "make certain that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field.").

Dr. Hecht placed the higher doses in context, addressing the seminal Magee and Barnes study and exposing the fallacy of the entire line of questioning:

> I don't know what you mean by "no correlation." This was, as you know, as you're well aware, the first study showing that dimethylnitrosamine causes liver tumors in rats. So naturally, they started with a high dose. That's -- if you don't start with a high dose, then you get a negative result and you still haven't answered the question.
>
> If you start with a high dose and you get a negative result, you can be pretty sure that the compound is not a strong carcinogen. Years later, as you know, after literally many, many studies have extended and confirmed this initial study showing that dimethylnitrosamine causes liver cancer in rats, there was the study -- the dose response study by Peto, Grasso and others -- showing going down to extremely low doses.

(Dr. Hecht Dep. Tr., 119:24-120:23).

Dr. Hecht also clarified that the animal data, including the Peto study data regarding low to high doses of NDMA and NDEA, is relevant here even separate and apart from the defense's focus on extrapolation, "I wouldn't say it doesn't provide any reliable information…it does give a strong indication of the strength of the carcinogen and a widely accepted animal model." (Dr. Hecht Dep. Tr., 123:23-124:18). Dr. Hecht also described the strong correlation between animal and human mechanistic data, another important part of the animal studies, i.e., "NDMA requires metabolism in order to be carcinogenic… Herron and Shank showed that humans metabolize NDMA to these DNA adducts the same way rats do." (Dr. Hecht 8/17/21 Dep. Tr., 448:13-451:22, 460:4-462:9, 464:5-466:5).

In this context, the defense draws a false equivalence between Dr. Hecht's approach and the clearly distinguishable facts and analysis in *Soldo v. Sandoz Pharms. Corp.*, 244 F. Supp. 2d 434 (W.D. Pa. 2003). In that case, the Court first discussed the Third Circuit's decision in *In re TMI Litig.*, 193 F.3d 613 (3d Cir. 1999), *as amended*, 199 F.3d 158 (3d Cir. 2000). As recited in *Soldo*, in *TMI* the Court criticized an expert's subjective methodology that could not be tested, where actual negative experiments performed on humans undermined the opinions and the expert failed to modify the opinions in response to that negative data without explanation. *Soldo*, 244 F. Supp. 2d at 529, *(*citing *TMI*, 193 F.3d 613, at 675-76). The Court went on to specify that the problems with the "assumption-based conclusions" of the plaintiff experts in relying on animal studies administering far higher doses than would be administered through use of the drug in question was that the experts (1) failed to explain how the studies were relevant, and (2) failed to provide any basis to think that the same results would occur at lower doses in line with the actual exposure levels. That is not the case here. For example, as quoted above, (1) it does give a "strong indication of the strength of the carcinogen," and (2) in this case unlike in *Sordo* there is animal

data predicated on low doses, "**If you want to get to human dose, you have to look at the Peto study**." (Dr. Hecht 8/17/21 Dep. Tr., 67:10-75:1).

In addition, in *Soldo*, the Court was unwilling to accept the opinions based on animal studies where there was no "'scientifically valid link' such as supporting human data." *Soldo*, 244 F. Supp. 2d at 546 (citing *Cavallo v. Star Enterprise,* 892 F. Supp. 756,762 (E.D. Va. 1995), *aff'd in part, rev'd in part on other grounds,* 100 F.3d 1150 (4th Cir. 1996)). In this case on the other hand, there is human dietary data showing statistically significant increases in cancer, human mechanistic data showing that the mechanism causing cancer is the same for animals and humans, human occupational data showing statistically significant increases in cancer, and even the human epidemiology data relied on by the defense shows a statistically significant increased risk for liver cancer (Gomm), and substantial increased risks (albeit not statistically significant) for colorectal and uterine cancer (Pottegård). The Court similarly cited to *Allen v. Pennsylvania Engineering Corp.*, 102 F.3d 194 (5th Cir. 1996), where the Court excluded opinions based on animal studies that were "inconclusive at best," there was "no evidence of the level of plaintiff's exposure," and "no epidemiological study has found a statistically-significant link between exposure to the substance and cancer." *Soldo*, 244 F. Supp. 2d at 547. Again, none of those issues exist here, where the animal studies demonstrate that NDMA and NDEA are consistently carcinogenic across species, the exposure levels are known, and the dietary studies, occupational data, and human epidemiology all show statistically significant links between exposure and cancer. Moreover, statistical significance is not an outcome determinative talisman. "A causal connection may exist despite the lack of significant findings, due to issues such as random misclassification or insufficient power…. A standard based on replication of statistically significant findings obscures the essential issue: a causal connection. Given this, the requisite proof necessary to establish

causation will vary greatly case by case." *Zoloft*, 858 F.3d at 794. In this case, there is substantial proof across multiple categories of relevant scientific evidence, and a scientific consensus that NDMA and NDEA are probable human carcinogens.

Dr. Hecht also confirmed the significance of the consistency of the data from the animal studies with the other categories of scientific evidence. For example, addressing the dietary cohort studies, "when you have these cohort studies that are showing a positive result and that positive result is consistent with what we know from experimental studies in animals, it is very compelling." (Dr. Hecht Dep. Tr., 446:12-447:6). And he did the same in correlating the animal studies to the mechanistic evidence as part of his "weight of evidence analysis." (Dr. Hecht Dep. Tr., 447:21-448:3).

Defendants ignore this convergence of findings, and instead try to distract with the false claim that the valsartan human epidemiology studies contradict the animal studies, and that Dr. Hecht ignored those studies. As a threshold, **Pottegård recognizes that "NDMA is one of the most well characterized and most potent animal carcinogens known and has been shown to be a potent carcinogen across all species that have been investigated, both as single doses and with long term exposure to lower quantities…NDMA 'should be regarded for practical purposes as if it were carcinogenic to humans**.'" (Pottegård, Kristensen, Ernst, Johansen, Quartarolo, & Hallas, *Use of N-nitrosodimethylamine (NDMA) contaminated valsartan products and risk of cancer: Danish nationwide cohort study*, B.M.J. 362., 1 (2018), Ex. 24)

The Defendants also blatantly mischaracterize the Pottegård and Gomm studies as studying "valsartan users as compared to a cohort of non-valsartan users." (Defs.' Br. at 40). In fact, the studies (both of which were short term and acknowledged the need for longer follow up to capture a truer picture of the resulting cancers) were designed to measure the outcomes for people taking

assumed contaminated valsartan, as compared to a cohort of people taking assumed non-contaminated valsartan (Gomm, Röthlein, Schüssel, Brückner, Schröder, Hess, Frötschl, Broich, & Haenisch, *N-Nitrosodimethylamine-Contaminated Valsartan and the Risk of Cancer—A Longitudinal Cohort Study Based on German Health Insurance Data*, DTSCH. ARZTEBL INT. 118, 358, 359 (2021), Ex. 25; Pottegård at 2 5). And this presents one of the design flaws that undercut the data, since the cohorts of users of assumed non-contaminated valsartan likely included people who used contaminated valsartan. (Dr. Hecht Report at 16-17; Dr. Hecht Dep. Tr., 474:16-480:19).[9]

Notwithstanding, Dr. Hecht explicitly considered this data (Dr. Hecht Report at 16-17), and demonstrated his familiarity with and analysis of the data during his deposition. This included for example the small sample size and follow up in Pottegård, refuting the suggestion by the defense that one of the negative findings in Gomm was not explicitly mentioned in his report (after acknowledging that by oversight he didn't explicitly mention a negative finding he was well aware of in Pottegård), and discussing the study design flaw arising from the concern that the not-exposed cohort actually included people who took contaminated valsartan. (Dr. Hecht Dep. Tr., 273:17-274:17, 286:21-287:5, 474:16-480:19).

Moreover, as stated, Pottegård showed increased risk for colorectal and uterine cancer, and Gomm showed a statistically significant increased risk for liver cancer. Thus, this is not a case where, "animal studies cannot overcome the contrary results of human epidemiological studies." *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 176 F. Supp. 3d 483, 494 (E.D. Pa. 2016). Dr. Hecht confirmed that the human epidemiologic data does not prove "that the animal

[9] Defense expert Dr. Catenacci also conceded this design flaw and that this raised questions about the validity of the findings. (Pls.' Br. in Supp. of Their *Daubert* Mot. to Preclude Opinions of Def. Expert Daniel Catenacci, p. 10).

data should be disregarded," and there is no study he is aware of that concludes either NDMA or NDEA are not human carcinogens. (Dr. Hecht Dep. Tr., 490:24-491:16). And here, we also have the consistent human dietary studies, occupational literature, and human mechanistic evidence.

The defense also focuses on statements in certain of the animal studies that the data should not be directly extrapolated to humans, as if that is a basis on which to ignore this important category of relevant scientific evidence. Dr. Hecht did not perform a risk analysis mathematically extrapolating the results of the animal studies to humans; however, the importance of those studies cannot be reasonably disputed by anyone. In fact, the FDA established its limits based on a risk assessment utilizing the Peto data, and the defense's own expert Dr. Johnson built his competing "PDE" limits based on the exact same animal data. (FDA, *Control of Nitrosamine Impurities in Human Drugs: Guidance for Industry*, p. 1 (Feb. 2021), https://tinyurl.com/2p8uxyyb, Ex. 26; Dr. Johnson Report at 59-60, Ex. 27). As stated in Dr. Hecht's report with regard to the animal studies, "A consistent and linear pharmacokinetic and metabolic pattern emerged in these studies resulting in the conclusion that extrapolation to humans of conclusions obtained in studies using laboratory animals was justified." (Dr. Hecht Report at 8). The animal data is clearly a significant, necessary piece of the puzzle in this case.

C. Endogenous NDMA Formation and Background Risk.

Defendants also falsely suggest that Dr. Hecht did not consider the background risk and the potential endogenous (inside the body) formation of NDMA. Dr. Hecht actually utilized peer-reviewed literature and quantified the levels of background nitrosamines in his report, "The highest levels were found in tobacco products (16,100 ng/g), followed by personal care products (1500 ng/g), while the lowest amounts were found in food and beverages (6.7 ng/g). Maximum average exposure to nitrosamines was estimated at about 25 ug per day, driven mainly by use of tobacco

products." (Dr. Hecht Report at 7). Also, in addressing the limits set by the EMA, "thresholds consistent with the FDA's thresholds, factoring in the potential for nitrosamines to exist due to background levels for example in water." (Dr. Hecht Report at 16). Moreover, Dr. Hecht considered the dietary study data—studies in which calculated levels of exogenously NDMA were superimposed on the background exposure levels, and demonstrated statistically significant increased risks for various cancers, for example with consumption as low as 120 ng of NDMA. (Dr. Hecht Report, at 14-16).

Dr. Hecht clearly testified to taking background levels into account, including the difficulty in establishing that there is endogenous formation of NDMA or NDEA, or in what amount. (Dr. Hecht Dep. Tr., 195:3-197:19). In this context, Defendants misrepresent that Dr. Hecht agreed "that peer-reviewed literature suggests that endogenous formation of NDMA and NDEA occurs at high levels exceeding exogenous intake." (Defs.' Br. at 46). The question cited did not mention NDMA and NDEA. Instead, it focused on "endogenous formation of **nitrosamines**," in general. (Dr. Hecht Dep. Tr., 190:13-22). In addressing this and one of the studies cited in his report that touched upon "endogenous formation of nitrosamines," Dr. Hecht explained that the data regarding endogenous formation of nitrosamines comes from noncarcinogenic nitrosamines, not from NDMA and NDEA which are metabolized and thus cannot have their levels measured for endogenous formation. "We do know that there's very solid research that some nitroso compounds are formed endogenously. These are nitrosamines such as nitrosoproline that are not metabolized, so we can actually track their formation in humans by measuring them in urine because they're not metabolized. But NDMA and NDEA present a different problem because they are metabolized, so it's very difficult to track their formation in humans… Nitrosoproline and some related nitros amino acids, that's where all the reliable endogenous formation data comes from and

those compounds are noncarcinogenic because they're not metabolized. They're excreted unchanged because they're polar." As Dr. Hecht succinctly stated, "We don't have good data on the endogenous formation of the compounds found in valsartan, dimethylnitrosamine." (Dr. Hecht Dep. Tr., 185:13-187:4; 191:19-193:6, 193:14-194:8, 195:9-19, 197:8-198:19). Thus, this is a subject that Dr. Hecht clearly took into account, based on reasoned scientific analysis.

Defendants also stretch their attack to try to capitalize on the inconsequential fact that nobody has done a specific study to test and establish whether "a modest one to seven percent increase in nitrosamine concentrations over a limited period of time would cause cancer in humans." For background, that hypothetical was constructed and calculated by defense counsel for Mylan in an effort to address the increased risk due to exposure from Mylan's contaminated valsartan, starting with an assumed mean NDEA level of 0.47 ppm, which converted to 150 ng. (Dr. Hecht Dep. Tr., 180:8-182:7). In building to the question, defense counsel then addressed data from a single study suggesting that non-smokers would consume nitrosamines (not just NDEA which is where the questioning started) of "about 2,000 nanograms per day," a level actually exceeded in the contaminated valsartan sold by multiple Defendants. The question posed was then focused on whether there are any, "studies that establish a one to seven percent increase in baseline nitrosamine consumption will lead to cancer in humans," and Dr. Hecht simply agreed that he is not aware of such a study, "in the setting that you just described." (Dr. Hecht Dep. Tr., 182:8-184:15). Of course, as the defense well knows, it is not necessary to conduct a study emulating the exact mode and dose of exposure at issue in order to present a valid general causation opinion. *Talcum*, 509 F. Supp. 3d at 179. Moreover, one could not ethically administer NDEA doses as stated in the hypothetical since that would be more than 5 times the maximum level of NDEA permitted by the FDA

D. Defendants' Arguments Go to the Weight of the Opinions, at Most.

The Defendants' arguments, primarily based on mischaracterizations of Dr. Hecht's opinions and testimony, go to the conclusions reached and the weight to be given those conclusions, at most. However, the focus of the reliability inquiry is on the expert's principles and methodology, not on his conclusions. *Glynn v. Merck Sharp & Dohme Corp.*, Nos. 11–5304, 08–08, 2013 WL 1558690, at *2 (D.N.J. April 10, 2013) (citing *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 594-95 (1993)) (Ex. 28). The basis for this Court's finding that an expert should be precluded under *Daubert* in another case demonstrates by comparison why Dr. Hecht's opinions should not be impacted here. *Player v. Motiva Enterprises LLC*, No. Civ. 02–3216(RBK), 2006 WL 166452, at *6-7 (D.N.J. Jan. 20, 2006) (citations omitted) (Ex. 15). In *Player*, this Court found an expert failed to satisfy the reliability requirement, as the expert failed to consider important facts without satisfactory explanation, among other things, and held: "His method is untestable and arbitrary, without a generally accepted, established, or peer-reviewed methodology, and his evaluation was conducted without any real standards." *Id.* at *7-8. None of those criticisms apply to Dr. Hecht's methodology, heavily weighted to peer-reviewed literature.

CONCLUSION

For the foregoing reasons, Defendants' motion to preclude Dr. Hecht's opinions, which are methodologically sound, should be denied.

Respectfully,

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CERTIFICATE OF SERVICE

I hereby certify that on December 1, 2021, I electronically filed a partially redacted version of this brief and my supporting certification with the Clerk of the Court using CM/ECF system which will send notification of such filing to the CM/ECF participants registered to receive service in this MDL. In addition, I hereby certify that unredacted copies of foregoing document will be served contemporaneous to filing via email on the Court, Special Master, and the Defense Executive Committee at DECValsartan@btlaw.com.

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Dated: December 1, 2021